DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

MEMORANDUM OF INDUSTRY MEETING

DATE: September 4, 2002

IND: [redacted]

Drug: atazanavir

Sponsor: Bristol-Myers Squibb (BMS)

BETWEEN:

Representatives from BMS

Sangeeta Agarwala, Ph.D., Sr. Research Investigator, Clinical Discovery
Richard Colonno, Ph.D., Vice President, Infectious Disease Drug Discovery
Roger Echols, M.D., Vice President, Infectious Disease Clinical Design and Evaluation
Michael Giordano, M.D., Group Director, HIV Clinical Design and Evaluation
Thomas Kelleher, Ph.D., Principal Statistician, Biostatistics and Programming
Thomas Mably, Ph.D., Director, Drug Safety Evaluation
Claude Nicaise, M.D., Vice President, Regulatory Science
Edward O'Mara, M.D., Director, Clinical Discovery
Phillip Pierce, M.D., Executive Director, Global Pharmacovigilance – Antivirals
Cynthia Piccirillo, Director, Regulatory Science Lead
Steven Schnittman, M.D., Vice President, Clinical Global Development
Lois Sechler, Ph.D., Associate Director, CMC-Regulatory Science
Laurie Smaldone, M.D., Sr. Vice President, Regulatory Science
Raul Soikes, Associate Director, Project Planning and Management
Richard Wilber, M.D., Executive Director, HIV Clinical Design and Evaluation

AND:

Representatives from FDA

Mark Goldberger, M.D., M.P.H., Director ODE IV
Debra Birnkrant, M.D., Division Director, DAVDP
Jeffrey Murray, M.D., M.P.H., Deputy Division Director, DAVDP
Stanka Kukich, M.D., Medical Team Leader, DAVDP
Kendall Marcus, M.D., Medical Reviewer, DAVDP

Thomas Hammerstrom, PhD., Biometrics Reviewer, DAVDP
David Roeder, Associate Director Regulatory Affairs, ODE IV
Kuei-Meng, PhD., Pharmacology/Toxicology Reviewer, DAVDP
George Lunn, PhD., Chemistry Reviewer, DAVDP
Narayana Battula, Microbiology Reviewer, DAVDP
Laura Pincock, Regulatory Review Officer, DDMAC
Greg Soon, PhD., Biometrics Team Leader, DAVDP
Julian O'Rear, PhD., Microbiology Team Leader, DAVDP
Lisa Naeger, PhD., Microbiology Reviewer, DAVDP
Kellie Reynolds, PharmD., Clinical Pharmacology Team Leader, DAVDP
Jenny Zheng, PhD., Clinical PharmacologyReviewer, DAVDP

SUBJECT: Industry Pre-NDA Meeting

BACKGROUND:

The Sponsor requested a pre-NDA meeting (SN 296 submitted June 19, 2002) and submitted a Pre-NDA briefing package (SN 302 submitted July 11, 2002) and a list of questions to be discussed during the meeting. The purpose of the meeting is to discuss the Sponsor's proposed registrational package for atazanavir capsules for the treatment of HIV-1 infection. The FDA responses are represented in italics.

DISCUSSION:

1) The NDA for atazanavir is based on two adequate and well-controlled trials, AI424034 (48-week report) and AI424043 (24-week report), and a number of supportive studies

- Does the Agency agree that the proposed submission package will be adequate in scope to support an indication for treatment of HIV-1 infection in combination with other antiretroviral agents?

  The proposed submission package is adequate in scope to support filing an NDA. Whether it is adequate in scope to support an indication for the treatment of HIV-1 infection is a review issue. Sponsor agreed.

2) At the End-of-Phase II meeting on April 17, 2001, and reflected in the minutes thereof (dated May 24, 2001), the Agency indicated that atazanavir "does offer a potential advantage over other currently available therapies due to its low pill burden, its potential lack of effect on serum lipid concentrations, and its potential role for use in antiretroviral treatment-experienced and highly treatment-experienced subjects. As a result, barring any additional safety concerns, the Division believes BMS-232632 could be a reasonable candidate for accelerated approval."

- Based on the reasons listed above, does the Agency agree that the atazanavir NDA will be a candidate for priority review? (It is understood that a final decision on this will be rendered at the filing meeting post-submission.)

Based on the above considerations, the atazanavir NDA may be a candidate for priority review. However, it is important to be aware that this NDA will likely be taken to an advisory committee meeting due to the safety concerns (hyperbilrubinemia, cardiac profile and any other potential risks that may arise during the review). Sponsor Agreed

- If the Agency does grant a priority review, when and how should BMS plan to submit additional safety data during the review?

  If the Agency grants a priority review, additional safety data can be submitted as an updated safety review no later than two months into the review clock. Sponsor Agreed.

3) Appended to this Pre-NDA Background Document is the statistical plan for the second pivotal study, AI424043. This plan projects to analyze data from the 300 randomized subjects received as of late September 2002 for the NDA submission. The protocol target of 220 randomized subjects will have received at least 24-weeks of treatment and the additional 80 randomized subjects will have received at least 16-weeks of treatment. BMS proposes to submit the 48-week analysis, i.e. analysis of data for all 300 randomized subjects receiving at least 48-weeks of treatment, as a post-approval commitment.

- Does the Agency find the proposed analysis planned for Study AI424043 acceptable for submission of the NDA?

  The Agency is okay with the Sponsor sending in initial 24 week data, then the remaining data sets can be sent in February 2003. Sponsor Agreed.

4) A fax was recently received from the Agency (dated June 5, 2002) regarding requested efficacy analyses for studies -034 (naive subjects) and -043 (treatment-experienced subjects, DAVDP primary endpoint) using a revised definition of virologic failure. These analyses will be submitted as a Response to the fax, and not included in the clinical study reports

This fax stipulates calculation of response rates for each visit through 48 weeks.

- Since we will not have 48-week data for study 043 at the time of the atazanavir NDA submission, BMS was not planning to apply this algorithm to the 24-week data. Does the agency agree?
  The Agency agrees.

5) Appended to this pre-NDA Background Document is a list of information which will become available during the review of the atazanavir NDA (Appendix 8).

- Which of this information does the Agency want submitted to the atazanavir NDA during review?

- In order not to be considered a major amendment to the NDA, and thus affect the user fee review clock, please advise on the logistics and acceptable timing for submission of this information.

  We would like to see all the information, as it becomes available. We are particularly interested in seeing data from the placebo controlled trial evaluating the effect of atazanavir on the PR and QT interval. We would like to see this study report submitted to us during the first two months of the review clock; if it is not received in the first three months it may be considered a major amendment to the NDA. Sponsor Agreed.

6) This Pre-NDA Background Document describes the planned safety analyses for the atazanavir NDA and appended is the Integrated Analysis Plan to support the registration of atazanavir, which includes the safety analyses of Phase II/III studies. Also described in the Background Document are specific safety considerations identified during the atazanavir development program.

- Does the proposed NDA for atazanavir provide adequate information to define the overall safety profile of ATV?

  The information provided by the proposed NDA appears to be adequate to define the overall safety profile of atazanavir; however, final determination of the adequacy of this information is a review issue.

- Will the proposed NDA for atazanavir provide adequate information to evaluate the following safety considerations:
  ~Hyperbilirubinemia and the absence of hemolysis or hepatotoxicity?

  The information appears to be adequate.

  ~Cardiac conduction?

  The information appears to be adequate; however, timely submission of the placebo controlled study may be important to prevent extension of the review clock. Please also be aware that we would like to see all ECG data submitted as data sets. Sponsor agreed

  ~ Lactic acidosis/symptomatic hyperlactemia?

  The information appears to be adequate.

  ~Absence of hyperlipidemia?

  The information appears to be adequate

  ~Drug interactions?

  In general, the information appears to be adequate.

The Sponsor has no plans at this time to conduct 1A2 or 2C9-inhibitor studies, nor any drug interaction studies involving warfarin, theophylline, amprenavir, indinavir, nelfinavir, or statins.

8) The NDA for atazanavir will present 26 clinical pharmacology studies (see Table 3.1A).

- Does the agency agree that the clinical pharmacology program will be adequate to support registration of atazanavir?

The program appears adequate to support registration; however, we would like to see PK/PD data from phase 2 studies, study 045, and any other PK/PD data from other phase 3 trials. We would also like to see previously requested PK/PD data such as the QT-c interval and all PK/PD analysis of the following studies in vitro metabolism, protein binding, and permeability study in human PK section. Please submit individual dissolution data and dissolution analysis summary in human PK section. The Sponsor agreed.

The following technical questions are included for purposes of identifying questions and responses in the official record and may be answered outside of the Pre-NDA meeting via appropriate means (teleconference, e-mail, etc.).

9) This Pre-NDA Meeting Background Document describes our formal electronic submission

- Is this submission acceptable to the review team?

  The submission appears acceptable.

- Are the reviewers agreeable to the proposal of providing a CTD Clinical Summary in place of the Summary of Human Biopharmaceutics (Item 6) and the Integrated Summaries of Efficacy and Safety (Item 8)?

  Yes, CTDs are acceptable in place of integrated summaries of Efficacy and Safety.

10) We propose to provide case report forms for deaths and discontinuations due to adverse events for all BMS sponsored studies. We do not intend to submit case report forms for the studies sponsored external to BMS. The case report forms for ongoing studies are provided through the database lock for the NDA analysis. These database locks range from July-2002 (for -034) to October-2002 (for -043).

- Is this acceptable to the review team? *Yes*

11) Per the special safety reporting agreement for atazanavir, certain adverse events are reported in an expedited fashion for subjects who have discontinued treatment Eight weeks prior to the event, rather than the usual four weeks.

- Should case report forms be included in the NDA for deaths and discontinuations due to adverse events using the 8 week or 4 week criteria for these certain adverse events?

  The $\leq$ 8 week criteria should be used for adverse events that were previously agreed would be submitted using the $\leq$ 8 week criteria.

12) BMS proposes to provide text narratives for all deaths and SAEs regardless of relationship to test drug and adverse events of special interest leading to discontinuation of treatment.

- Is this acceptable to the review team? *Yes*

13) BMS requests a waiver for submission of paper review copies of all technical sections of the NDA, including case report forms and case report tabulations. Paper review copies of the Labeling and Application Summary will be provided.

- Is this acceptable to the review team?

  No, we would like to see paper copies of all sections except for the CRTs and CRFs.
  The Sponsor agreed.

If this is not acceptable, we request a waiver for submission of paper review copies for reports in the NDA that were previously submitted, as well as case report forms and case report tabulations?

- Is this acceptable to the review team?

  No, we would like to see all reports submitted with the NDA and we would like to see paper copies of the reports. The Sponsor agreed.

14) Does the review team have a preference or suggestion for the mechanism for pre-submission of currently available study reports? (The currently available study reports are those reports in the NDA TOC identified with a BMS document control number and a version number, see Appendix 1).

We would like to see all completed study reports as soon as possible. We would also like to see samples SAS programs and data as soon as possible. The Sponsor agreed.

Action:

1. The Sponsor agreed to all terms mentioned above.
2. The Sponsor agreed to have a follow-up teleconference to discuss technical issues relating to submission.
3. The Sponsor agreed to use microbiology's template for submission of their resistance data (gentotypic & phenotypic).
4. The sponsor agreed to send available pharmacokinetics studies before NDA submission.

/S/

Minutes Prepared by:
Vasavi Reddy, RPh., LT, USPHS
Division of Antiviral Drug Products

See Attachments:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Date of Meeting: **July 20, 2001**

IND: [redacted]

Drug: **Atazanavir (BMS-232632)**

Indication: **Treatment of HIV-1 infection**

Sponsor: **Bristol-Myers Squibb Company (BMS)**

Type of Meeting: **Discussion of Serious Adverse Event (SAE) Reporting**

FDA Attendees:
Debra B. Birnkrant, M.D., Acting Division Director, DAVDP
Jeffrey S. Murray, M.D., Acting Deputy Director, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP
Kendall Marcus, M.D., Medical Officer, DAVDP
Joseph G. Toerner, M.D., Medical Officer, DAVDP
Kimberly Struble, Pharm.D., Regulatory Review Officer, DAVDP
Kellie S. Reynolds, Pharm.D., Pharmacokinetics Team Leader, DAVDP
Anthony DeCicco, R.Ph., Chief Project Manager, DAVDP
Destry Silllivan, MS, Regulatory Project Manager, DAVDP
Karen A. Young, RN, BSN, Regulatory Project Manager, DAVDP

BMS Attendees:
Todd F. Baumgartner, M.D., Executive Director, Regulatory Sciences
Roger Echols, M.D., Vice President, Infectious Diseases Clinical Research
Louis Ferrara, B.S., Director Regulatory Science
Thomas Kelleher, Ph.D., Sr. Research Biostatistician/Biostatistics & Data Management
Claude Nicaise, M.D., Vice President/ Regulatory Science
Steven Schnittman, M.D., Group Director, HIV Clinical Research
Susan Rosen, Director, Medical Surveillance and Epidemiology
Kenneth Kassler-Taub, M.D., Vice President, Worldwide Safety and Surveillance
Sydney Kahn, Executive Director, Medical Surveillance and Epidemiology
Deborah Dehertogh, M.D., Executive Director, Infectious Diseases Research and Development
Doug Roberts, Director, Drug Safety Evaluation and Pharmacovigilance

Background

The death of patient 040-154 enrolled in Study AI424-008 was identified through a MedWatch report to the stavudine NDA. This death was not reported to IND —— On June 15, 2001, the Division sent a letter to Bristol-Myers Squibb (BMS) to address our expectations regarding the reporting of serious adverse events (SAEs). Upon reviewing submission serial number 176 dated July 10, 2001, two additional deaths of patients enrolled in studies of atazanavir were identified that occurred shortly after the subjects discontinued antiretroviral therapy; these deaths also had not been reported to IND —— After learning of these two additional deaths, the Division requested a teleconference to discuss SAE reporting. Since many BMS representatives were at the Agency for a scheduled pre-NDA meeting, a face-to-face meeting was held. Other BMS representatives, not present at the pre-NDA meeting, participated via teleconference.

Discussion

As outlined above, the Division is aware of serious adverse events and deaths that have not been reported to IND —— These cases highlight the Division's concerns that BMS is not appropriately reporting SAEs and deaths.

The Sponsor stated that they did not have a full understanding of the reporting process. According to BMS, if an SAE is evaluated and considered not related to the investigational drug, it does not meet the Code of Federal Regulations' (CFR) requirement for immediate reporting. BMS planned to report all of these SAE's in the IND annual report. We outlined our expectation that all SAEs occurring in study subjects participating in an atazanavir clinical trial be reported to IND —— in a timely fashion, regardless of causality. Moreover, it was emphasized that while the study investigator and Sponsor make a determination of the relatedness of the event to the investigational drug, the reviewers must also have the opportunity to make a determination of causality. In addition, we need to have all information available in order to determine the relationship between an SAE and an investigational drug. With investigational drugs, it is the Division's belief that it is prudent for the Sponsor to utilize a conservative approach when interpreting SAEs.

The Sponsor expressed concern about the volume of paperwork that SAE reporting to study investigators would generate and its effect on the study site. If study investigators receive information on all SAEs, then there may be a tendency to overlook an important letter that the Sponsor may send. BMS suggested future discussions with the Division after an internal discussion. The Division agreed to discuss SAE reporting to investigators and investigational review boards (IRBs) at a later date. At this time, the Division's primary issue was the notification of all SAEs to the Division.

The Sponsor brought to the Division's attention a report faxed to the Division regarding stavudine reports of motor weakness with or without hyperlactatemia among 11 patients receiving stavudine in combination with other antiretrovirals. Five of these cases occurred in subjects enrolled in investigational studies sponsored by Bristol-Myers Squibb; four of these five subjects died despite discontinuation of medications. Bristol-Myers Squibb believes that these cases may represent a signal for a previously unrecognized toxicity. They will be

conducting an extensive literature search for similar reports and seeking input from relevant outside experts.

Summary/Action Items

1. The Sponsor agrees to submit all SAEs and deaths that occur in atazanavir studies, regardless of causality, and in the time frame outlined in 21 CFR 312.32.

2. The Sponsor will submit a proposal that will address reporting of safety information to IRBs and study investigators.

3. The Division will provide in a telephone facsimile our request for submission and analysis of SAEs and deaths.

4. The Division will consult OPDRA and evaluate the adverse event of serious motor weakness potentially associated with stavudine.

Minutes Preparer: _____ Date: _____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Date of Meeting: April 17, 2001

IND: [redacted]

Drug: BMS-232632

Indication: Treatment of HIV-1 infection

Sponsor: Bristol-Myers Squibb Company (BMS)

Type of Meeting: End-of-Phase 2 Meeting

FDA Attendees:
Debra B. Birnkrant, M.D., Acting Division Director, DAVDP
Jeffrey Murray, M.D., Acting Deputy Director, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP
Kendall Marcus, M.D., Medical Officer, DAVDP
Joseph G. Toerner, M.D., Medical Officer, DAVDP
Theresa Wu, M.D., Medical Officer, DAVDP
Kuei-Meng Wu, Ph.D., Pharmacologist, DAVDP
Jenny H. Zheng, Ph.D., Pharmacokinetics Reviewer, DAVDP
Kellie S. Reynolds, Pharm.D., Pharmacokinetics Team Leader, DAVDP
George Lunn, Ph.D., Chemist, DAVDP
Julian O'Rear, Ph.D., Acting Microbiology Team Leader, DAVDP
Narayana Battula, Ph.D., Microbiologist, DAVDP
Gregory Soon, Ph.D., Acting Statistical Team Leader, DAVDP
Tom Hammerstrom Ph.D., Mathematical Statistician, DAVDP
Mary Parks, M.D., Medical Team Leader, DMEDP
Antoine El-Hage, Ph.D., Phamacologist, Branch Chief, DSI
David L. Roeder, M.S., Associate Director for Regulatory Affairs, ODEIV
Christine Lincoln, RN, MSN, MBA, Regulatory Project Manager, DAVDP
Karen A. Young, RN, BSN, Regulatory Project Manager, DAVDP

BMS Attendees:
Todd F. Baumgartner, M.D., Executive Director, Regulatory Sciences
Clifford Bechtold, M.A., Director, Project Planning and Development
Rene Belder, M.D., Executive Director/Metabolics Clinical Research
Richard Colonno, Ph.D., Vice President/Infectious Disease Discovery
Ann Cross, Ph.D., Director/Biostatistics and Data Management
Roger Echols, M.D., Vice President, Infectious Diseases Clinical Research
Louis Ferrara, B.S., Director Regulatory Science
Michael Giordano, M.D., Director/Infectious Disease Clinical Research
Thomas Kelleher, Ph.D., Sr. Research Biostatistician/Biostatistics & Data Management
Thomas Mably, Ph.D., Sr. Research Investigator/Drug Safety Evaluation
Vanaja Mummaneni, Ph.D., Sr. Research Investigator/Metabolism and Pharmacokinetics
Claude Nicaise, M.D., Vice President/ Regulatory Science
Edward O'Mara, M.D., Associate Director/Clinical Pharmacology
Laurie Smaldone, M.D., Sr. Vice President/Regulatory Science and Outcomes Research
Steven Schnittman, M.D., Group Director, HIV Clinical Research
Lois Sechler, Ph.D., Associate Director - CMC/Regulatory Science

Background
Bristol-Myers Squibb (BMS) provided a meeting background document dated March 17, 2001 (Serial Number 149) that included summary information from their Phase 1 and Phase 2 studies, clinical and registrational plans for Phase 3 development, and a list of points for discussion. Prior to the meeting, the Sponsor conveyed the following objectives for the end-of-Phase 2 meeting: 1) to reach an agreement on treatment-experienced trial designs, 2) to reach an agreement on the acceptability of BMS-232632 for an accelerated approval NDA filing and the content of the NDA package, and 3) to discuss the lipid results and the implications of these data for labeling.

Discussion
BMS began the meeting with a brief presentation on BMS-232632 that included an overview of the safety and efficacy data, lipid data and plans for Phase 3 registration. [redacted] After the presentation, the following issues as outlined by the Sponsor in the background meeting package were discussed. These points of discussion included: trial designs in treatment-experienced populations, accelerated approval, dose selection, hyperbilirubinemia associated with BMS-232632, and lipid profile labeling.

Treatment-Experienced Trial Designs
The Division had the following comments with regard to the proposed studies in treatment-experienced patients:

1. The Division encouraged the Sponsor to remove all CD4 restrictions as entry

requirements for their proposed clinical trials. If the Sponsor chooses to keep this restriction in the protocols, the drug will be indicated for use in patients with the stated CD4 parameters.

2. The Sponsor has considerable data from studies AI424-007 (007) and AI424-008 (008) that compare BMS-232632 to nelfinavir in treatment naïve patients. The Division believes that study AI424-037 (037) will provide limited information beyond what has been learned from these trials. Thus, the Division recommended that the Sponsor consider eliminating trial 037 and expanding either trial AI424-043 (043) or AI424-045 (045) for use as the second registrational trial to support approval. The Division acknowledges these clinical trials will be difficult to enroll, and will require an increase in sample size to be used for registration. The Division will discuss the number of subjects needed at a later date with the Sponsor.

   The Division acknowledged the difficulty in blinding these studies. In general, the open label design of trial 043 appears to be acceptable.

3. The Sponsor has not justified the choice of the 200 mg dose of ritonavir to be studied in study 045. The BMS-232632 AUC achieved with 200 mg is similar to that seen with 100 mg, and the C_{min} does not appear significantly different. It is likely that use of the 200 mg dose will result in a higher incidence of adverse events, without a clear benefit in terms of efficacy. In addition it was emphasized that because registrational trials need to be adequate and well-controlled, it is unlikely that this single-arm, uncontrolled study would provide results supportive of approval. The Division asked the Sponsor to consider the addition of a second arm to this study to evaluate the combination of BMS-232632 with ritonavir 100 mg. The two arms could be blinded to the dose of ritonavir.

4. The Division also requested that the Sponsor submit a plan for dose reduction in study 045 and provide justification for the exclusion of patients treated with regimens containing both non-nucleoside reverse transcriptase inhibitors (NNRTI) and a protease inhibitor (PI) at the time of enrollment.

Accelerated Approval

The Division does not feel that a once daily dosing schedule of an agent that must be given with food offers a significant advantage over currently available therapies. However, BMS-232632 does offer a potential advantage over other currently available therapies due to its low pill burden, its potential lack of effect on serum lipid concentrations, and its potential role for use in treatment experienced and highly treatment-experienced patients. As a result, barring additional safety concerns, the Division believes BMS-232632 could be a reasonable candidate for accelerated approval.

Twenty-four week data from two adequate and well-controlled trials are needed to

support an accelerated approval action. If BMS-232632 is given a priority review, it is important to have as much completed data as possible at the time of NDA submission. The data generated in the Phase 3 studies will determine how much additional data is needed.

Dose Reduction and Hyperbilirubinemia

The Division concurs with the selection of the 400 mg dose for Phase 3 studies. However, the Division has several concerns with the Sponsor's management strategy of dose reduction for Grade 4 hyperbilirubinemia. The complexity of the proposed approach was discussed. The Division pointed out that 48-week data supporting the safety and efficacy of dose reduction would likely be needed to support labeling recommendations. Safety and efficacy at the lower dose would need to be demonstrated, and should include resistance data. The Sponsor agreed to submit a detailed proposal for management of dose reductions.

Lipid Profile and Labeling

The Agency agrees BMS-232632 may potentially impact serum lipids to a lesser degree than currently marketed PI's. However, because data presented in the background package included both fasting and non-fasting samples, the reliability of those data is questionable. In Phase 3 trials, the Division recommends the Sponsor obtain fasting lipid evaluations and that they ascertain what proportion of patients require lipid lowering agents.

One suggestion discussed was the need for recording dietary intake given that imbalances in diet between the treatment arms could affect results. However, after discussion, it was decided the recording of dietary intake was not feasible.

Adverse event data from studies that include appropriate evaluations of changes in lipids may be included in labeling. The proposal to include this in the "CLINICAL STUDIES" section of the label is not acceptable. The appropriate text and/or tables could be included in the "ADVERSE EVENTS" section of the label.

Summary/Action Items

1. The Division believes that BMS-232632 may be an appropriate candidate for accelerated approval.

2. The Division will fax responses to the Sponsor's questions that were not addressed at the meeting (questions 3 and 10), as well as additional comments that were not addressed during the meeting.

3. The Division strongly encourages the Sponsor to consider alternative studies as a registrational trial to support traditional approval. The Division recommends that the

Sponsor increase the sample size of either study 043 or 045 and that the results from one of these trials could be used as a second registrational trial to support approval.

4. Given the restraints imposed by conducting a trial that is fully blinded, the proposed open label design for study 043 would be acceptable for a registrational trial.

5. If the Sponsor chooses to proceed with study 037, the Division concurs with the criteria for establishing superiority to nelfinavir as outlined in study 037.

6. The Division and Sponsor agree to have further discussion regarding the study design of studies 043 and 045.

7. The Sponsor agrees to remove the CD4 count study restrictions from all Phase 3 trials.

8. The Sponsor will submit a proposal for management of dose reduction due to hyperbilirubinemia. In addition, the Sponsor will submit PK/PD data on all study subjects who were "dose reduced".

9. The effect of BMS-232632 on lipids will likely be included in the "ADVERSE EVENTS" section of the label.

Minutes Preparer: _____ Date: _____

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Date of Meeting: May 18, 2000

IND: [redacted]

Drug: BMS-232632

Indication: Treatment of HIV-1 infection

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute (BMS)

Type of Meeting: Chemistry, Manufacturing and Controls (CMC)

FDA Attendees:
George Lunn, Ph.D., Chemist, DAVDP
Stephen Miller, Ph.D., Chemistry Team Leader, DAVDP
Joseph Toerner, M.D., Medical Officer, DAVDP
Sandra Suarez, Ph.D., Pharmacokinetics Reviewer, DAVDP
Melissa Truffa, R.Ph., Regulatory Project Manager, DAVDP

BMS attendees:
Michael Burnett, Director, CMC-Regulatory Science and Outcomes Research
Heba Guirgis, Technical Investigator, Pharmaceutics Technology and Development
Sherry Konrad, Manager, Regulatory Science
Nancy Lewen, Senior Research Scientist I, Analytical R&D
Mary Moran, Senior Scientist, Technical Operations, Chemical Development
Sandeep Modi, Documentation resources manager, Pharmaceutical Development Strategic Operations
Vanaja Mummaneni, Ph.D., Metabolism and Pharmacokinetics
Faranak Nikfar, Senior Research Investigator, Pharmaceutics R&D
Madhu Pudipeddi, Research Investigator Pharmaceutics R&D
Lois Sechler, Associate Director, CMC-Regulatory Sciences and Outcomes Research
Pankaj Shah, Associate Director, Analytical R&D
Sushil Srivastava, Associate Director, Process Technology
Satyam Upadrashta, Associate Director, CMC-Regulatory Sciences and Outcomes Research

Background
On April 18, 2000 (SN076), Bristol Myers Squibb (BMS) requested a meeting with the Division of Antiviral Drug Products (DAVDP) to discuss the CMC content of the proposed NDAs for BMS-232632-05. A pre-meeting package was included with this request that contained a list of questions for discussion. In addition, the sponsor submitted a copy of the slides that were to be used during the meeting on May 12, 2000 (SN080). The sponsor acknowledged receipt of DAVDP's comments from two May 15, 2000 facsimiles.

For each discussion topic, the sponsor's question is shown in regular font, followed by DAVDP's response in **bold** font.

Discussion

1. Is the proposed plan to qualify process changes during manufacture of the bulk drug substance from the Current Process to the Proposed Commercial Process adequate to support NDA filings?

   DAVDP recommends that the sponsor submit stability data for at least 3 batches from one site and 1 batch from the other site. We understand that release data will be available for 5 batches from each site. Impurities should be qualified from a toxicological perspective. We understand that drug substance manufactured using the proposed (commercial) process will be used for clinical trials.
   BMS agreed to submit an IND Amendment to propose that stability data from 2 batches of drug substance produced using the current process and 1 batch using the proposed (commercial) process will be submitted as primary NDA stability data to qualify the —— —— site. Stability data from at least one batch will be submitted for the Syracuse site. This IND Amendment will also discuss the timing of the NDA filing, stability updates, and statistical analyses.

2. [redacted]

3. [redacted]

4. Please comment on the acceptability of the capsule ——— dissolution methods.

   The capsule (Amendment 076, page 34) are acceptable from a CMC perspective. However, it is not clear that Q=—— at 45 min will be discriminatory for undergranulated capsules (Amendment 076, page 36). We understand that the acceptance criterion will probably be tightened to make the method discriminatory. For the ——— method we understand that the weight of —— dispensed for each test will be measured and that —— will be used as the analytical method. The Biopharmaceutics reviewers will make a final decision on the dissolution methods when all the data have been

submitted and reviewed. Any additional data that are requested should be submitted as an IND Amendment requesting FDA agreement on dissolution medium, stirring speed, and apparatus.

5. Please comment on the adequacy of plans for content uniformity testing for the

6. Are the bridging studies to qualify use of the Proposed Commercial Process material for capsule presentations adequate to support the NDA filing?

Yes. The impurities should be qualified from a toxicological standpoint. Drug substance from the proposed (commercial) process will be used in clinical trials.

7. Our intention is to submit 12 month stability data on three batches of the capsule dosage form using Current Process material; however, only 6 months stability data may be available on capsules made from the Proposed Commercial Process drug substance. Please comment on the acceptability of the 6-month stability data, at the time of the NDA filing, for the capsule products made from the Proposed Commercial Process material.

This is acceptable but a 9 month stability update should be filed for these batches during the NDA review period.

8.

9. BMS intends to add an additional manufacturing site for drug substance manufacturing in the NDA filing. At the time of the NDA filing, we will provide the following:
   - three months of accelerated stability data on one lot of drug substance made at this site on a pilot scale
   - evidence of API equivalency between sites.

   Prior to NDA approval, we will provide the following:
   - a certificate of analysis for one batch of API
   - commitment to place one batch of API made at commercial scale at the new site on long term stability.

   The Division assumes that the manufacturing procedure will remain the same. For each drug substance manufacturing site release data should be available, at the time of review, for at least 3 batches to establish equivalence. Additionally stability data for at least one batch should be available for each site. In this case a 6-month stability update should be filed for the stability batch. Each drug substance manufacturing site should have a commitment to place the first 3 commercial batches into the stability program. NDA batches that are commercial scale can count towards this. Please include in the NDA a detailed list of the manufacturing and testing facilities, their individual responsibilities, and information about when each site will be ready for inspection.

10. Does FDA agree with the BMS position that the materials identified are starting materials for the API Manufacturing process?

    Given that at least 3 vendors are available for the starting materials BMS-233110-01, BMS-217947-01, and BMS-214702-01 (Amendment 080, page 013) this is acceptable. Lists of vendors for each compound should be submitted with the NDA filing.

Other Discussions

11. [redacted]

12. BMS stated that current plans are for an NDA submission in 4Q 2001. If a pre-submission of the CMC data is planned, BMS should coordinate the timing with the submission of the clinical section of the NDA. In general, the CMC pre-submission should not be submitted more than 4 months prior to the NDA submission date.

Minutes Preparer:_____ Date: _____

Concurrence:
HFD-530/Chem/Lunn eso 6/16/00
HFD-530/ChemTL/Miller 5/26/00 eso SM
HFD-530/PM/Truffa 6/16/00

Distribution:
Original IND —— ' (SN 064 and SN 080)
Division file
HFD-530/PM/Truffa
HFD-530/Chem/Lunn
HFD-530/Chem/Miller
HFD-530/Suerez

IND —— May 18, 2000 (MR)

Meeting Minutes

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Date of Meeting: **March 7, 2000**

IND: [redacted]

Drug: **BMS-232632**

Indication: **Treatment of HIV-1 infection**

Sponsor: **Bristol-Myers Squibb Pharmaceutical Research Institute (BMS)**

Type of Meeting: **Clinical Development Meeting (Phase 2)**

FDA Attendees:
Heidi Jolson, M.D., M.P.H., Division Director, Division of Antiviral Drug Products (DAVDP)
Debra Birnkrant, M.D., Acting Deputy Director, Clinical, DAVDP
Walla Dempsey, Ph.D., Acting Deputy Director, Pre-Clinical, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP
Joseph Toerner, M.D., Medical Officer, DAVDP
Kuei-Meng Wu, Ph.D., Pharmacologist, DAVDP
James Farrelly, Ph.D., Pharmacology Team Leader, DAVDP
Sandra Suarez, Ph.D., Pharmacokinetics Reviewer, DAVDP
Kellie Reynolds, Pharm.D., Team Leader, Pharmacokinetics Team Leader, DAVDP
George Lunn, Ph.D., Chemist, DAVDP
Narayana Battula, Ph.D., Microbiologist, DAVDP
Tom Hammerstrom Ph.D., Mathematical Statistician, Division of Biometrics
John Senior, M.D., Medical Officer, DGCDP
Thomas Hassall, BS Pharm., MS, Associate Director for Regulatory Affairs, ODEIV
Melissa Truffa, R.Ph., Regulatory Project Manager, DAVDP
Charles Frost, Pharm.D., Visiting Post-Doctoral Fellow

BMS attendees:
Clifford Bechtold, M.S., Director, Project Planning and Development
Richard Colonno, Ph.D., Vice President/Infectious Disease Discovery
Ann Cross, Ph.D., Director/Biostatistics and Data Management
Roger Echols, M.D., Vice President, Infectious Diseases Clinical Research
Michael Giordano, M.D., Director/Infectious Disease Clinical Research
Thomas Kelleher, Ph.D., Sr. Research Biostatistician/Biostatistics and Data Management
Sherry Konrad, B.S., Manager, Regulatory Science
Thomas Mably, Ph.D., Diplomate, A.B.T., Sr. Research Investigator/Drug Safety Evaluation
Vanaja Mummaneni, Ph.D., Metabolism and Pharmacokinetics
Claude Nicaise, M.D., Vice President/ Regulatory Science

Edward O'Mara, M.D., Associate Director/Clinical Pharmacology
Sol Rajfer, M.D., Sr., Vice President/Clinical Research
Steven Schnittman, M.D., Group Director, HIV Clinical Research
Laurie Smaldone, M.D., Sr. Vice President/Regulatory Science

Background

Bristol-Myers Squibb (BMS) provided a meeting background document dated February 7, 2000 (Serial Number 064) that included summary information from their Phase 1 and Phase 2 studies, clinical and registrational plans for Phase 3 development, and a list of points for discussion. The original intent of this meeting was to discuss the End of Phase 2 development of BMS-232632; however, after review of the background document DAVDP determined that data adequate to support discussion of the design of Phase 3 trials were not available and reclassified this meeting as clinical development meeting. Comments outlining our concerns with the data submitted in the meeting package were conveyed to the sponsor in a facsimile dated March 3, 2000.

Discussion

To convene the meeting BMS acknowledged receipt of our comments from the March 3, 2000 facsimile. Based on these comments BMS suggested redirection of the focus of the meeting from the five questions included in the background document to a discussion of their overall clinical development program for BMS-232632. After a brief overview of their Phase 1 and Phase 2 programs, BMS proposed the following points for discussion:

1. **Accelerated Approval**: At a December 1998 meeting, BMS asked the Division if BMS-232632 in a once-daily dosing regimen would meet the criteria for Accelerated Approval (Subpart H) under 21CFR (314.510). BMS requested that the Division readdress the question at this time. At the time of our previous meeting, DAVDP indicated that a novel protease inhibitor with a once daily dosing schedule could qualify for accelerated approval under subpart H. However, after review of preliminary safety and efficacy data for BMS-232632, at this time we can not commit to an accelerated approval of an NDA because there are insufficient data to support dose selection or define the adverse events profile. Our safety concerns need to be addressed with longer-term data and additional studies. As more safety and efficacy data become available discussion of whether accelerated approval would be appropriate for BMS-232632 will continue.

2. **Safety/ hyperbilirubinemia**: BMS requested that the agency outline their specific safety concerns with BMS-232632. This prompted a presentation from Dr. John Senior, a hepatology consultant to the FDA review team, who reviewed the mechanism of indirect hyperbilirubinemia. Dr. Senior reiterated the Division's concern that a mechanism for the indirect dose-related hyperbilirubinemia associated with BMS-232632 has not yet been elucidated. The Division feels that compelling evidence should be provided demonstrating that indirect hyperbilirubinemia associated with BMS-232632 is not due to liver injury. The Division agreed to provide the sponsor with recommendations for additional studies that should be undertaken in order to adequately characterizing the mechanism(s) of indirect hyperbilirubinemia associated with BMS-232632.

3. **Dose selection**: BMS presented clinical pharmacokinetic data in healthy volunteers suggesting that the lowest dose (200 mg) of BMS-232632 currently being studied in HIV-infected patients would not achieve steady-state mean concentrations above protein binding-adjusted IC_{90} values

over the 24 hour dosing period. BMS proposed focusing their continued Phase2/Phase 3 clinical development on higher doses (400 mg and/or 600 mg). The Division, however, noted that preliminary data have not identified differences in antiviral activity among the multiple doses studied and that the elevations in bilirubin are dose-related. Therefore, it is the opinion of the Division that a safe and effective dose has not been identified. The choice of the 400 mg dose of BMS-232632 administered once daily as the appropriate dose does not appear to be justified based on currently available data. We recommend that the sponsor evaluate the 24-week activity and safety data from stage one of studies AI424-007 and AI424-009 prior to initiating larger studies. Furthermore, we do not believe that adequate justification for inclusion of the 600 mg dosing arm in study AI424-009 has been provided, particularly given that a high incidence of hyperbilirubinemia will be expected with the administration of this dose.

4. **Study Design**: The Division noted that the sponsor proposed to submit a minimum of 24 week safety and efficacy data from studies AI424-007, AI424-008, and AI424-009 in order to support marketing approval under the accelerated approval regulations. Potential concerns identified by the Division that would make these studies unsuitable as principal studies include the following:

   a. multiple comparator arms,
   b. multiple interim analyses planned for studies AI424-007 and AI424-009,
   c. open-label study design, and
   d. utilization of changes from baseline plasma HIV RNA as the study endpoint.

   We continue to recommend the use of the proportion of study patients with plasma HIV RNA below the level of detection as the primary endpoint for Phase 3 studies.

   Further clinical and statistical discussions on the design of Phase 3 studies will take place once a safe and effective dose of BMS-232632 has been identified. The Division agreed to review interim data from ongoing Phase 2 studies to facilitate these discussions.

Other Discussion Points from Background Document
(For each discussion point, the sponsor's question is shown in regular font, followed by FDA response in bold font.)

1. Is the clinical plan as outlined adequate to support the target indication in both adults *and* children (≥3 months of age)?

   The proposed plan is not adequate for the reasons discussed above with regard to safety, dose selection, and study design.

2. Is the clinical pharmacology plan as outlined adequate to support the target indication in both adults *and* children (≥3 months of age)?

   In general, the clinical pharmacology plan as outlined appears to be adequate; however, when a target dose for further study has been selected, the Division may have additional comments. If BMS 232632 will be combined with other protease inhibitors such as amprenavir or with non-nucleoside reverse transcriptase inhibitors such as nevirapine or delavirdine, the sponsor should conduct drug-drug interaction studies with these drugs.

3. With HIV clinical trials now utilizing phenotypic and genotypic resistance testing as part of enrollment standards, please comment on the consequence of this regarding product labeling.

DAVDP strongly encourages the use of baseline HIV resistance testing to optimize background therapy in trials conducted in treatment-experienced patients. This practice is consistent with current clinical practice and the recently updated Treatment Guidelines.

Additionally, we are aware that some sponsors may wish to make efficacy claims based on their drug's ability to treat patients with a particular resistance pattern at baseline. In this circumstance, the sponsor should propose the type of labeling claim that they wish to make, and they should then discuss with the Division, the type of clinical data that would be required to support the labeling claim.

4. BMS has recently initiated dose intensification of BMS-232632 for subjects failing 24-weeks, but who are otherwise tolerating drug, are compliant, and have phenotypic sensitivity to BMS-232632 ($\leq$2.5x EC_{50} of control strain). Please comment on how the outcome of these subjects should be evaluated.

Patients who initiated dose intensification of BMS-232632 because of a failing antiviral treatment regimen would be considered treatment failures in the primary analysis. As the development of BMS-232632 progresses, DAVDP and the sponsor will continue to discuss study design and exploratory analyses.

5. Is the ICH common technical document format acceptable for the non-clinical section of this NDA?

Discussion of the ICH common technical document format is premature at this time and would best be addressed at a future End of Phase 2 meeting or Pre-NDA meeting.

Summary/Action Items

1. BMS is committed to fully exploring the mechanism(s) of indirect hyperbilirubinemia associated with BMS-232632. DAVDP will provide the sponsor with recommendations for additional studies to adequately characterize the mechanism of hyperbilirubinemia associated with BMS-232632. BMS also indicated that they have no plans to study the concomitant administration of BMS-232632 and indinavir and would contraindicate concomitant use because of the overlapping safety profiles of these two protease inhibitors.

2. With regard to dose selection, the Division expressed an interest in reviewing additional data that will include a greater number of patients for a longer duration of dosing. It was agreed that the sponsor would submit interim data from ongoing Phase 2 studies for review by DAVDP.

3. The sponsor will provide the Division with proposals for simplified Phase 3 protocol designs and a plan of action for the continued clinical development of BMS-232632.

Minutes Preparer:_____ Date: _____

Concurrence:
HFD-530/MO/ Toerner edited 3/20/00, 4/5/00
HFD-530/MTL/Cvetkovich edited 3/22/00, 4/5/00
HFD-530/DivDir/Jolson edited 3/23/00, edited 5/4/00 eso HJ
HFD-530/PM/Truffa/ prepared 3/16/00 mmt
HFD-530/BPH/Suarez, edited 3/28/00 eso SS 3/28/00

Distribution:
Original IND ———
Division file
HFD-530/PM/Truffa
HFD-530/MO/Toerner
HFD-530/MTL/Cvetkovich
HFD-530/Jolson

IND ———/March 7, 2000 (MR)

Meeting Minutes

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: January 6, 2003	**DUE DATE:** March 6, 2003	**ODS CONSULT #**: 01-0193-3

TO: Debra B. Birnkrant, M.D.
Director, Division of Anti-Viral Drug Products
HFD-530

THROUGH: Vasavi Reddy
Project Manager, Division of Anti-Viral Drug Products
HFD-530

PRODUCT NAME:	**NDA SPONSOR:**
Reyataz (Atazanavir Sulfate Capsules) 100 mg, 150 mg, and 200 mg and and	**Bristol-Myers Squibb**

NDA: 21-567

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY:
In response to a consult request from the Division of Anti-Viral Drug Products (HFD-530), the Division of Medical Errors and Technical Support (DMETS) conducted a labeling review. DMETS has attempted to focus on safety issues relating to minimizing possible medication errors.

DMETS RECOMMENDATION:
DMETS recommends implementing the label and labeling revisions found in Section II of this review in order to minimize potential user error.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PRE-MARKETING LABELING REVIEW

DATE OF REVIEW: February 20, 2003

NDA #: 21-567

NAME OF DRUG: **Reyataz**
(Atazanavir Sulfate Capsules)
100 mg, 150 mg, and 200 mg
and

NDA SPONSOR: Bristol-Myers Squibb

I. INTRODUCTION:

This consult is in response to a January 6, 2003, request from the Division of Anti-Viral Drug Products for a review of the labeling for the proprietary name, Reyataz. "Reyataz" was originally found acceptable by the Division of Medication Errors and Technical Support (DMETS) on November 1, 2002,
(ODS consult # 01-0193-2). At that time, DMETS requested that the Division forward the labels and labeling for review and comment 90 days prior to approval of the drug.

PRODUCT INFORMATION

Reyataz is the proposed proprietary name for atazanavir capsules Reyataz is an azapeptide inhibitor of HIV-1 protease. Reyataz was being evaluated for use in combination with other anti-retroviral agents for the treatment of HIV infections. It will be available in 100 mg, 150 mg, and 200 mg capsules, and dosed once daily. The capsules will be available in bottles of 60 and the

II. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container label and package insert labeling for Reyataz Capsules, DMETS has attempted to focus on safety issues relating to possible medication errors, and has identified areas of possible improvement, which might minimize potential user error.

A. General Comments

2 page(s) of revised draft labeling has been redacted from this portion of the review.

III. RECOMMENDATIONS

DMETS recommends implementing the label and labeling revisions, as outlined in Section II of this review, in order to minimize potential error.

- DMETS would appreciate feedback on the final outcome of this consult. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina R. Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tia Harper-Velazquez
3/10/03 03:11:26 PM
PHARMACIST

Jerry Phillips
3/10/03 03:19:50 PM
DIRECTOR

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: Aug 16, 2002	**DUE DATE:** Oct 16, 2002	**ODS CONSULT #:** 01-0193-2

TO: Debra B. Birnkrant, MD
Director, Division of Anti-Viral Drug Products
HFD-530

THROUGH: Vasavi Reddy
Project Manager, Division of Anti-Viral Drug Products
HFD-530

PRODUCT NAME:	**NDA SPONSOR:**
Reyataz (Atazanavir Capsules 100 mg, 150 mg, and 200 mg **IND:**	**Bristol-Myers Squibb**

SAFETY EVALUATOR: Kevin Dermanoski, RPh

SUMMARY:
In response to a consult from the Division of Anti-Viral Drug Products, (HFD-530), the Division of Medication Errors and Technical Support (DMETS), conducted a review of the proposed proprietary name, Reyataz, to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS has no objection to the use of the proprietary name Reyataz. This name along with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 25, 2002

IND#

NAME OF DRUG: Reyataz
(Atazanavir Capsules
100 mg, 150 mg, and 200 mg

IND SPONSOR: Bristol-Myers Squibb

I. INTRODUCTION:

This review is in response to a request from the Office of Anti-Viral Drug Products, to review the proprietary name Reyataz, regarding potential name confusion with other proprietary/established drug names. The container labels, carton labeling and package insert labeling for Reyataz were not submitted and thus were not reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Reyataz is the proposed proprietary name for atazanavir capsules . This is the second proprietary name submission. The sponsor originally submitted the name however, DMETS did not recommend the use of that name (see consult 01-0193-1). Reyataz is an azapeptide inhibitor of HIV-1 protease. Reyataz is being evaluated for use in combination with other anti-retroviral agents for the treatment of HIV infections. It will be available in 100 mg, 150 mg, and 200 mg capsules, and dosed once daily. The capsules will be available in bottles of 60 and the

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike Reyataz to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Reyataz. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified Fortaz, ——————— as having the potential for confusion with "Reyataz." These products are listed in Table I, along with the dosage forms available and usual dosage.

2. The Expert Panel also noted that Reyataz sounds similar to the dosage form Reditabs (e.g., Claritin *Reditabs*).

3. DDMAC did not express concerns regarding the name Reyataz.

Table I: Potential Sound-Alike and/or Look-Alike Names Identified by DMETS Expert Panel for Reyataz

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Reyataz	**Atazanavir Capsules and Oral Powder** **100 mg, 150 mg, and 200 mg** **50 mg/1.5 g**	**400 mg once daily.**	
Fortaz	Ceftazidime for Injection 500 mg/vial, 1 g/vial, 2 g/vial, 6 g/vial Ceftazidime for Injection in Plastic Container Eq 20 mg base/mL, Eq 40 mg base/mL	Dependent on patient and disease variables. Usual range: 250 mg q12h to 2 g q8h; maximum dose of 6 g/day	S/A
[redacted]			

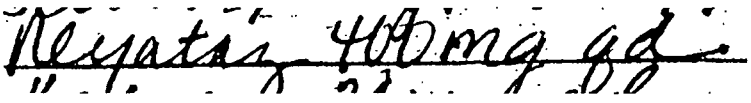
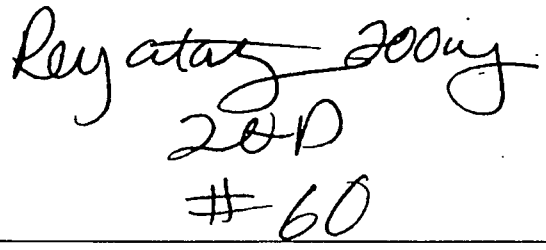
*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

B. PRESCRIPTION ANALYSIS STUDIES

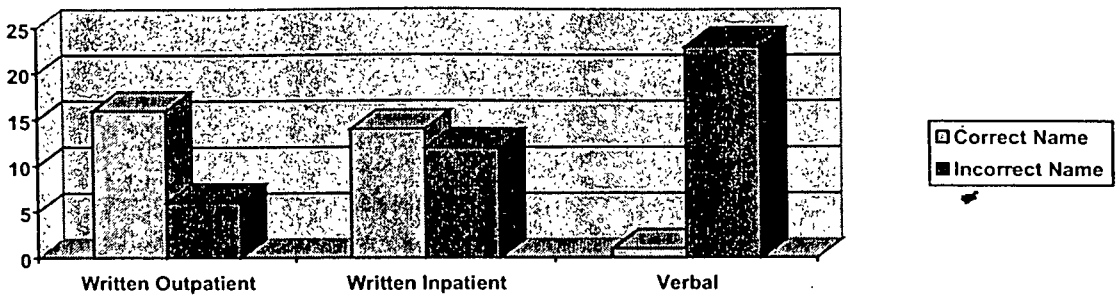
1. Methodology:

Three studies were conducted within FDA for the proposed proprietary name Reyataz to determine the degree of confusion with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed 102 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An outpatient prescription and inpatient order were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Reyataz (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, a verbal order was recorded on voice mail. The voice mail message was then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient Rx #1: 	This prescription is for Reyataz 200 mg, dispense 60, with the directions to take two capsules daily.
Outpatient Rx 	

2. Reyataz results are summarized below.

Study	# Of Participants	# Of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Outpatient	31	22 (71%)	16 (73%)	6 (27%)
Written Inpatient	32	26 (82%)	14 (54%)	12 (46%)
Verbal	39	24 (62%)	1 (4%)	23 (96%)
Total	102	72 (71%)	31 (43%)	41 (57%)



Sixteen (73%) of the 22 respondents in the written outpatient study interpreted the name correctly. The 6 incorrect interpretations were

Fourteen (54%) of the 26 respondents in the written inpatient study interpreted the name correctly. The 12 incorrect interpretations were

One (4%) of the 24 respondents in the verbal inpatient prescription study interpreted the name correctly. The 23 incorrect interpretations were

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Reyataz; Fortaz, Ery-tab, and Rynatan were identified as having the greatest potential for causing medication errors due to name confusion with Reyataz. Additionally, the EPD panel noted that Reyataz sounded similar to the dosage form Reditabs (e.g., Claritin *Reditabs*). However, the panel also noted that the potential for medication errors due to name confusion between Reyataz and the modifier Reditabs was reduced because practitioners commonly prescribe the proprietary name Claritin and add the formulation, *Tablets* or *Reditabs*, to differentiate the two products. Thus the likelihood of the Reditabs modifier being prescribed only, is minimal.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Reyataz was confused with Fortaz, Ery-tab, or Rynatan. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed name, Reyataz.

Fortaz (Ceftazidime) is a semi-synthetic, broad-spectrum, beta-lactam antibiotic for parenteral administration. Fortaz is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms. Fortaz and Reyataz may sound-alike depending upon how they are pronounced. Each name shares the final syllable "taz" which increases their sound-alike similarities. However, the number of syllables per name (2 vs. 3) and the first three letters ("For" vs. "Rey") are two factors that reduce their sound-alike potential. There are also product differences that reduce the potential for medication errors due to name confusion. Fortaz and Reyataz differ in route of administration (parenteral vs. oral), dosing interval (twice daily vs. once daily), dosage form (injectable vs. capsule/powder for oral use), packaging (vials or I.V. bags vs. bottles), and are not likely to be stored

near each other on pharmacy shelves. Overall, the product differences reduce the risk for medication errors due to name confusion between Fortaz and Reyataz.

Ery-tab (erythromycin delayed-release tablets) is an antibacterial product containing erythromycin base in a special enteric-coated tablet that protects it from inactivation in gastric acidity and permits absorption of the antibiotic in the small intestine. Ery-tab is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms. Ery-tab and Reyataz may sound-alike depending upon pronunciation. The names share similar sounds and the same number of syllables. Although both products are anti-infectives, Ery-tab is an anti-bacterial while Reyataz is an anti-viral. There are additional product differences that reduce their potential to cause medication errors due to name confusion. The products differ in dosage form (tablet vs. capsule/powder for oral use), dosing interval (2, 3, or 4 times daily vs. once daily), duration of therapy (short term vs. chronic), and share no overlapping strengths (250 mg, 333 mg, and 500 mg vs. 100 mg, 150 mg, and 200 mg). Additionally, the products will likely not be stored near each other on pharmacy shelves. Overall, the product differences reduce the risk for medication errors due to name confusion between Ery-tab and Reyataz.

Rynatan (azatadine maleate and pseudoephedrine sulfate) is a combination product available by prescription only to treat allergic rhinitis and upper respiratory congestion. Rynatan is a distributor name under the NDA application for Trinalin. Rynatan and Reyataz are seven-letter, three-syllable names that may look alike depending upon how they are scripted (see below). The initial syllable of each name (Ryn and Rey) begins with "R" and contains the letter "y." In addition, three out of four final letters in each name appear in the same sequence (ata). Rynatan and Reyataz overlap in routes of administration and may be dispensed in the same quantity (e.g., a script for "#60" may often be a 1-month supply of each product). However, there are product differences that reduce the potential for medication errors. Rynatan and Reyataz differ in dosing intervals (twice daily vs. once daily) and formulation (tablet vs. capsules). Rynatan is a combination product available in only one strength (1 mg/120 mg). In contrast, Reyataz will be available in three strengths (100 mg, 150 mg, and 200 mg); therefore prescriptions for Reyataz will require the listing of a specific strength. Additionally, the Rynatan strength does not overlapp with any of the strengths of Reyataz. This helps distinguish the products and reduce the potential for medication errors due to name confusion. Overall, the product differences reduce the risk for medication errors due to name confusion between Rynatan and Reyataz.

Rynatan	Reyataz
Rynatan	Reyataz

III. RECOMMENDATIONS:

DMETS has no objection to the use of the proprietary name Reyataz.

This name along with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Kevin Dermanoski, RPh Date
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kevin Dermanoski
10/29/02 10:43:10 AM
PHARMACIST

Denise Toyer
10/31/02 12:29:41 PM
PHARMACIST

Carol Holquist
10/31/02 12:47:45 PM
PHARMACIST

Jerry Phillips
11/1/02 10:48:49 AM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and echnical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM:
Vasavi Reddy, RPh., LT., USPHS
Regulatory Project Manager, HFD-530
Division of Antiviral Drug Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6 Jan 03		21-567		20 Dec 02

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
	Yes	HIV/Protease Inhibitor	Within reasonable time/Application on 6-month clock

NAME OF FIRM: Bristol-Meyers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
'PE A OR B NDA REVIEW .D OF PHASE II MEETING CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Note: Please See EDR for NDA submission regarding carton and labeling proposals. See attached for proposed PI.
AC Meeting being scheduled for 13 May 2003 (concerns that will be addressed: QT prolongation, Bilirubinemia)
45-day filing meeting scheduled for 27 Jan 03 from 10-11

PDUFA DATE: 20 June 2003
ATTACHMENTS: Draft Package Insert, Container and Carton Labels

...chival IND/NDA #####
HFD-###/Division File
HFD-###/RPM
HFD-###/Reviewers and Team Leaders

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)

	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Acrobat Document

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Cardio-Renal Drug Products (HFD-110)
Project Manager: Wendy Lail
Assigned Medical Reviewer: Shari Targum

FROM:
Vasavi Reddy, RPh, Regulatory Project Manager
Division of Antiviral Drug Products (HFD-530)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Oct 2, 2002	——— (SN 337)			September 20, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
atazanavir		Antiviral	October 31, 2002

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ■ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ PE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

1. Please comment on the necessity of this trial in view of current plans to obtain extensive ECG data from subjects in phase 3 clinical trials.
2. Please comment on the general design of this study and provide us with any recommendations you may have to optimize the data obtained from this study.

Additional request:
-Would you be able to participate in a teleconference with the sponsor to discuss the design of this protocol?

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Associate Director, Medication Error Prevention
Office of Post Marketing Drug Risk Assessment, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM:
Vasavi Reddy, Regulatory Project Manager
Division of Antiviral Drug Products/HFD-530

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
14 Aug 2002	—		Request for review of proposed Trade Name	9 August 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Atazanavir (BMS-232632)		Protease Inhibitor, Antiretroviral	When appropriate. Sponsor plans to submit NDA Dec. 2002

NAME OF FIRM: Bristol-Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: The sponsor is requesting a review by the FDA's Office of Post-Marketing Drug Risk Assessment of their proposed trade name (Reyataz).

Please see attached copy of the submission for additional information.**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Cardio-Renal Drug Products (HFD-110)
Project Manager: Wendy Lail
Assigned Medical Reviewer: Shari Targum

FROM:
Vasavi Reddy, RPh, Regulatory Project Manager
Division of Antiviral Drug Products (HFD-530)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7/31/02	~~~			July 12, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
atazanavir		Antiviral	Aug.30, 2002

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ■ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the following materials summarizing the evaluation of atazanavir and its effect on the QT and PR interval. If approved, atazanavir will be used as a 400 mg once daily dose, and in a "ritonavir enhanced" regimen as atazanavir 300 mg and ritonavir 100 mg.

1) Do you think that there is any significant risk for development of torsades de pointe with these two dosing regimens?
2) If so, do you have any specific suggestions as to how to convey this information in labelling?
3) Do you think that atazanavir induced PR prolongation may lead to any clinical significant cardiovascular events(None clearly related to PR prolongation have been reported during clinical trials)?
4) Do you have any further suggestions for evaluation of atazanavir with regards to QT and PR prolongation?

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Helen S. Barold, M.D.
J Corporate Blvd., HFZ-450
Rockville, MD 20850

FROM:
Karen A. Young, Regulatory Project Manager
Division of Antiviral Drug Products
HFD-530 301-827-2376

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 15, 2001	~~~	N/A	IND	July 10, 2001, Serial # 176

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Atazanavir (BMS-232632)		Protease Inhibitor	60 days Contact person: Dr Marcus, X7-2361

NAME OF FIRM: Bristol Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- X SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

X CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
There is a clear dose related prolongation of PR interval, and less clear prolongation of the QT interval. Please evaluate the effect of atazanavir on the QT and PR interval and comment on safety and any further evaluation that you feel that is warranted. Thank you!

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kendall Marcus, M.D., Medical Officer, DAVDP	☐MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Associate Director, Medication Error Prevention
Office of Post Marketing Drug Risk Assessment, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM:
Karen A. Young, Regulatory Project Manager
Division of Antiviral Drug Products
HFD-530, N 418 301-827-2376

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/17/01			Request for review of proposed Trade Name	9/5/01

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Atazanavir (BMS-232632)		Protease Inhibitor, Antiretroviral	When appropriate. Sponsor plans to submit NDA mid 2002

NAME OF FIRM: Bristol-Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: The sponsor is requesting a review by the FDA's Office of Post-Marketing Drug Risk Assessment of their proposed trade name [redacted] Background: BMS is beginning Phase 3 trials for Atazanavir. Atazanavir is an indictable drug intended for oral administration of 400 mg daily for treatment of HIV infection. This will be a chronic dosing regimen and the first protease inhibitor with once daily dosing. The earliest anticipated submission date for a NDA would be 2nd quarter 2002. Besides the drug name, the sponsor provided limited drug information. If you have any questions, please feel free to call or e-mail. Will send via interoffice mail Sponsor's submission (SN 202) with request. Please note that there is discussion among the review team that the generic name be changed in the order to prevent potential medication errors between zanamivir and atazanavir.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Norman Stockbridge, Ph.D., M.D., Team Leader
Division of Cardio-Renal Drug Products
HFD-110, WOC 2

FROM:
Karen A. Young, Regulatory Project Manager
Division of Antiviral Drug Products
HFD-530 301-827-2376

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 17, 2001	—	N/A	IND	July 10, 2001, Serial # 176

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Atazanavir (BMS-232632)		Protease Inhibitor	August 15, 2001 Contact person: Dr Marcus, X7-2361

NAME OF FIRM: Bristol Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
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- ☐ RESUBMISSION
- X SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
. PE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

X CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Clear dose related prolongation of PR interval, and less clear prolongation of the QT interval. Over 1000 patients have been dose with no obvious cardiac events. Please advise on risk and evaluation.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kendall Marcus, M.D., Medical Officer, DAVDP	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:

Margaret Simoneau, Project Manager
PKLN, HFD-510
301-827-6411

FROM:

Karen A. Young, Regulatory Project Manager
Division of Antiviral Drug Products
HFD-530 301-827-2469

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 21, 2001			Background document for EOP2 industry meeting	March 19, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
BMS-232632	End of Phase II industry meeting scheduled on 4/17.	Protease Inhibitor	April 13, 2001

NAME OF FIRM: Bristol-Myers Squibb Company

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- X END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We are requesting a consultant who is available to attend both an industry meeting (on April 17, 2001 at 2pm) and the pre-industry meeting (on April 13, 2001 at 12 noon). The Sponsor will claim that the protease inhibitor, BMS-232632 does not cause the lipid abnormalities that are often seen with other protease inhibitors. Since the Sponsor plans to bring a consultant to discuss this lack of lipid effect, we would like to have a consultant available to address questions in this area.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Diane Weber
Bristol-Myers Squibb Pharmaceutical
Research Institute
P.O. Box 5400
Princeton, NJ 08543

2. TELEPHONE NUMBER *(Include Area Code)*

(609) 252-5167

3. PRODUCT NAME

atazanavir

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-567

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NDA 21-567

(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4439

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☑ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Cynthia F. Piccirillo	Director, Regulatory Science	December 20, 2002

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

USER FEE VALIDATION SHEET

NDA # 21-567 Supp. Type & # N000 UFID # _____
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO **User Fee Cover Sheet Validated?** **MIS_Elements Screen Change(s):**

2. (YES) NO **APPLICATION CONTAINS CLINICAL DATA?**
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.**

3. YES (NO) **SMALL BUSINESS EXEMPTION**

YES (NO) **WAIVER GRANTED**

5. YES (NO) **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).**
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO **BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required**
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. (P) S **PRIORITY or STANDARD APPLICATION?**

/S/ 12/30/02
PM Signature / Date

/S/ 12.30.02
CPMS Concurrence Signature / Date

2/14/00

/ –

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-567 _____ - _____

Drug: REYATAZ (atazanavir capsules) Applicant Bristol-Meyers Squibb

RPM Vasavi Reddy, RPh Phone (301) 827-2413

☐505(b)(1) X
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: Priority

Pivotal IND(s) —

Application classifications:
Chem Class 1
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary : June 20, 2003
Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: **X** User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... X AP AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... Included
  Original proposed labeling (package insert, patient package insert) ..... Included
  Other labeling in class (most recent 3) or class labeling.....
  Has DDMAC reviewed the labeling? .....Pending review Yes (include review) ☐No
  Immediate container and carton labels ..... Most recent included
  Nomenclature review ..... Included

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application **is not** on the AIP.

  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review)

- Post-marketing Commitments — Included
  - Agency request for Phase 4 Commitments..... N/A
  - Copy of Applicant's commitments ..... Included

- Was Press Office notified of action (for approval action only)?..... Y
  - Copy of Press Release or Talk Paper.....

- Patent
  - Information [505(b)(1)] ..... Included
  - Patent Certification [505(b)(2)]..... N/A
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... Included

- Exclusivity Summary ..... Included

- Debarment Statement ..... Included

- Financial Disclosure
  - No disclosable information ..... Included
  - Disclosable information – indicate where review is located ..... N/A

- Correspondence/Memoranda/Faxes ..... Included

- Minutes of Meetings ..... Included
  - Date of EOP2 Meeting Yes
  - Date of pre NDA Meeting Yes
  - Date of pre-AP Safety Conference draft included

- Advisory Committee Meeting ..... Held
  - Date of Meeting ..... May 13, 2003
  - Questions considered by the committee ..... Included
  - Minutes or 48-hour alert or pertinent section of transcript ..... Included

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... included

- Clinical review(s) and memoranda ..... draft included

Continued ⇨

- ♦ Safety Update review(s) ..... Included

- ♦ Pediatric Information
  x Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... Included
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted xNot Applicable

- ♦ Statistical review(s) and memoranda ..... Included

- ♦ Biopharmaceutical review(s) and memoranda..... draft included

- ♦ Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... N/A

- ♦ Microbiology (efficacy) review(s) and memoranda ..... draft included

- ♦ DSI Audits ..... included
  x Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ CMC review(s) and memoranda ..... Final included

- ♦ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

- ♦ DMF review(s) ..... N/A

- ♦ Environmental Assessment review/FONSI/Categorical exemption ..... Included

- ♦ Micro (validation of sterilization) review(s) and memoranda ..... N/A

- ♦ Facilities Inspection (include EES report)
  Date completed Pending review. See CMC Exec Summary ..... Acceptable ☐ Not Acceptable

- ♦ Methods Validation ..... ☐ Completed X Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ Pharm/Tox review(s) and memoranda ..... draft inlcuded

- ♦ Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

Demographic Worksheet

Application Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21,567 Submission Type: N/A (pilot) Serial Number: N/A (pilot)

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	1700	All Females	828	Females >50	40
Age:	0-≤1 Mo.	0	>1 Mo.-≤2Year	6	>2-≤12	23
	12-16	13	17-64	2510	≥65	17
Race:	White	1104	Black	502	Asian	151
	Other	771				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was gender-based analysis included in labeling? Yes	No
Efficacy	☑ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☑
Safety	☑ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☑

Is a dosing modification based on gender recommended in the label? No — ☐ Yes ☑ No

If the analysis was completed, who performed the analysis — ☑ Sponsor ☑ FDA

Age-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was age-based analysis included in labeling? Yes	No
Efficacy	☐ Yes	☑ No	☑ Inadequate #'s	☐ Disease Absent	☐	☑
Safety	☐ Yes	☑ No	☑ Inadequate #'s	☐ Disease Absent	☐	☑

Is a dosing modification based on age recommended in the label? ☐ Yes ☑ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was race-based analysis included in labeling? Yes	No
Efficacy	☑ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☐
Safety	☑ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☐

Is a dosing modification based on race recommended in the label? ☐ Yes ☑ No

If the analysis was completed, who performed the analysis ☑ Sponsor ☑ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided fo why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug mi be altered (including if labeling was modified).

Comment: